PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
CDM/P61500/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/03686	22.08.2003	23.08.2002
International Patent Classification (IPC) or both national classification and IPC		
C07H21/00		
Applicant		
SOLEXA LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2004	14.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer de Nooy, A Telephone No. +31 70 340-2338

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03686

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-116 as originally filed

Claims, Numbers

1-50 as originally filed

Claims, Pages

117, 118 received on 23.11.2004 with letter of 23.11.2004

Drawings, Sheets

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-2 (in part), 3-4 (in full), 5-11 (in part), 12-28 (in full), 29-50 (in part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-2 (in part), 3-4 (in full), 5-11 (in part), 12-28 (in full), 29-50 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-2, 5-11, 29-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2, 8, 11, 31-33, 37-39
	No:	Claims	1, 5-7, 9-10, 29-30, 34-36, 40-50
Industrial applicability (IA)	Yes:	Claims	1-2, 5-11, 29-50
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Note that this examination is only for claims 1-2, 5-11, 29-50 (all in part) for which the modified nucleotide or nucleoside is as claimed in claim 1 where Z is -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 with R4, R5 and R6 as in Figure 3 (as filed with the letter of 23 November 2004; note that the other amendmends of claim 1 in this letter are not examined here since they have not been searched), and methods and kits pertaining thereto, since no search report was established for the other parts of the claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: WO0229003

Novelty
The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-2, 5-11, 29-50 is new in the sense of Article 33(2) PCT. In the prior art no document is disclosed containing nucleosides or nucleotides having an -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 3'-O protecting group with R4, R5 and R6 as in Figure 3.

Inventive step
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 does not involve an inventive step in the sense of Article 33(3) PCT.
The document D1 is regarded as being the closest prior art to the subject-matter of claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 and discloses modified nucleosides for use in sequencing reactions using polymerases. The subject matter of those claims differs from D1 in that instead of the -CH2-O-CH3 protecting group of D1 (see figures and claims), -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 as protecting groups with R4, R5 and R6 as in Figure 3 are claimed.
The problem to be solved by the present invention may therefore be regarded as provision of a further compounds for use in a sequencing reaction.

The solution proposed in claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
In order to solve the above problem, the skilled man would look for other protection-deprotection strategies. Having knowledge of D1, the skilled man would modify the protective group by adding a substitution in the form of an -O-R6 or -S-R6. In order to contain an inventive step, the applicant should show that those different protecting groups have an advantage over the ones of D1.

CLAIMS

1. A modified nucleotide or nucleoside molecule comprising a purine or pyrimidine base and a ribose or deoxyribose sugar moiety having a removable 3'-OH blocking group covalently attached thereto, such that the 3' carbon atom has attached a group of the structure

-O-Z

wherein Z is any of $-C(R^{IV})_2-O-R''$, $-C(R')_2-N(R'')_2$, $-C(R')_2-N(H)R''$, $-C(R^{IV})_2-S-R''$ and $-C(R')_2-F$,

wherein $-C(R^{IV})_2-O-R''$ is of the formula $-CR^4(R^5)-O-CR^4(R^5)-OR^6$ or of the formula $-CR^4(R^5)-O-CR^4(R^5)-SR^6$; and wherein $-C(R^{IV})_2-S-R''$ is of the formula $-CR^4(R^5)-S-CR^4(R^5)-OR^6$ or of the formula $-CR^4(R^5)-S-CR^4(R^5)-SR^6$;

wherein each R" is or is part of a removable protecting group;

each R' is independently a hydrogen atom, an alkyl, substituted alkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, acyl, cyano, alkoxy, aryloxy, heteroaryloxy or amido group, or a detectable label attached through a linking group; or $(R')_2$ represents an alkylidene group of formula $=C(R''')_2$ wherein each R''' may be the same or different and is selected from the group comprising hydrogen and halogen atoms and alkyl groups;

each R^4 and R^5 is independently a hydrogen atom or an alkyl group;

R^6 is alkyl, cycloalkyl, alkenyl, cycloalkenyl or benzyl; and

wherein said molecule may be reacted to yield an intermediate in which each R" is exchanged for H or, where Z is $-C(R')_2-F$, the F is exchanged for OH, SH or NH_2, preferably OH, which intermediate dissociates under aqueous conditions to afford a molecule with a free 3'OH; with the proviso that where Z is $-C(R^{IV})_2-S-R''$, both R^{IV} groups are not H.

2. A molecule according to claim 1 wherein R' is an alkyl or substituted alkyl.

3. A molecule according to claim 1 or claim 2 wherein -Z is of formula $-C(R')_2-N_3$.

4. A molecule according to any one of claims 1 to 3 wherein Z is an azidomethyl group.

5. A molecule according to claim 1 or claim 2 wherein R" is a benzyl or substituted benzyl group.

6. A molecule according to any preceding claim wherein said base is linked to a detectable label via a cleavable linker or a non-cleavable linker.

7. A molecule according to claim 6 wherein said linker is cleavable.

8. A molecule according to any one of claims 1 to 5 wherein a detectable label is linked to the molecule through the blocking group by a cleavable or non-cleavable linker.

9. A molecule according to any one of claims 6 to 8 wherein said detectable label is a fluorophore.

10. A molecule according to any one of claims 6 to 9 wherein said linker is acid labile, photolabile or contains a disulfide linkage.

11. A modified nucleotide molecule as claimed in any one of claims 1 to 10 which comprises one or more ^{32}P atoms in its phosphate portion.

12. A nucleoside, nucleotide or polynucleotide